

## Adipose-Derived Stem Cells for Hip Osteoarthritis: A Promising Case Series

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### Abstract

**Introduction:** Osteoarthritis is a degenerative disease with increasing incidence due to the world's population aging. It presents with pain and articular dysfunction, with a frequent tendency to progress. Medical and surgical approaches to osteoarthritis are evolving towards less invasive and more advanced, cell-based strategies. Adipose-derived stem cells represent a promising innovative tool. Relevant attention in the medical literature has been dedicated to the application of this therapy, particularly in the hip joint. However, little has been reported on this approach for the hip. We present our institutional retrospective case series on adipose-based treatment of hip osteoarthritis.

**Methods:** Twenty-eight hips in twenty-four consecutive patients suffering from osteoarthritis were treated between October 2016 and May 2020 with adipose-based intraarticular hip injection. Hip scores were retrospectively reviewed through analysis of hospital charts. The adipose tissue was processed with a mechanical nonenzymatic method proven to be effective in isolating adipose-derived stem cells and stromal vascular fraction. Candidates for this treatment were considered all patients non-responsive to conservative treatment and with grade II-III according with Kellgren-Lawrence radiographic score. Patients were assessed preoperatively, and at 6, 12 and 18-month post-treatment using a visual analogue pain scale (VAS) and Harris hip score (HHS) to quantify the pain and the function.

**Results:** The mean pre-operative VAS-based pain score was  $6.3 \pm 1.1$  and showed significant improvement at 6 months. At 12 and 18 months the VAS score maintained a good outcome which was  $3.2 \pm 2.2$  and  $3.4 \pm 2.3$  respectively. All scores at 6, 12, and 18 months of follow-up showed a statistically significant improvement ( $p < 0.01$ ) compared to baseline. The mean pre-operative Harris hip score (HHS) was  $65.9 \pm 2.6$ , the mean 6 month  $83.7 \pm 7.7$ , the mean at 12 months  $82.5 \pm 8.8$ , and the mean at 18 months  $81.5 \pm 6.8$ . Good or excellent results were recorded in twenty hips at final follow-up. There was no statistical difference between the group Kellgren-Lawrence II and III in term of VAS or HHS score at 6, 12 and 18 months. Five patients underwent hip arthroplasty at the final follow up, two of them having good results at 12 months. Four hips had unsatisfactory results at 6 months.

**Conclusions:** adipose-based infiltrative treatment of hip degenerative disease is a promising, relatively easy and safe technique. More research is necessary to consolidate these findings.

**Keywords:** hip, OA, AD-MSC, intra-articular injections, stem cells.

### List of Abbreviations

**VAS:** visual analogue pain scale

**HHS:** Harris hip score

**AD-MSC:** Adipose-derived mesenchymal stem cells

### Introduction

Osteoarthritis is a degenerative disease with increasing incidence due to the world's population aging. It represents one of the commonest causes of disability for the elderly

[1]. It presents with pain and articular dysfunction, with a frequent tendency to worsen over time. The hip is the second most frequently affected joint after the knee, in terms of osteoarthritis and other degenerative conditions. The prevalence of symptomatic hip OA was reported at 9.2% among adults age 45 years and older, with 27% showing radiologic signs of disease [2]. The lifetime risk for symptomatic hip OA is 18.5% for men and 28.6% for women [3]. Gender, age and genetics are individual intrinsic risk factors, while obesity, articular stress and a history of trauma are extrinsic risk factors [4]. The local

pathophysiological inadequate response to this is synovial hypertrophy combined with remodelling of the subchondral bone [5,6]. Due to its avascular nature, cartilage has no or little regeneration tendency, thereby evolving to a progressive diminution of chondrocytes, synovitis and pain. To address the critical need for new therapies and the limited approach to this problem, in the last few years a new technique with mesenchymal stem cells (MSC), harvested from abdominal adipose tissue, has been developed with the aim of decreasing pain and improving quality of life.

## MSC

The role of mesenchymal stem cells (MSCs), with their inherent ability to differentiate along different cell lines of mesodermal lineages (including osteoblasts and chondrocytes) coupled with their observed paracrine expression of several growth factors and cytokines which promote tissue repair and reduce inflammation, are of increasing interest [7]. Medical and surgical approaches to osteoarthritis are evolving towards less invasive and more advanced, cell-based strategies. Adipose-derived stem cells represent a promising innovative tool. Attention in the medical literature has been dedicated to the application of this therapy particularly in the knee joint. However, little has been reported on this approach for the hip joint. We present our institutional retrospective case series on adipose-based treatment of hip joint. This retrospective study will assess the practicality and appropriateness of hip injections with Adipose-derived stem cells (AD-MSC).

## Materials and methods

A retrospective analysis of collected data was conducted at a single centre for all patients treated with adipose-based stem cell (AD-MSC) intraarticular hip injection between October 2016 and May 2020 by a single surgeon (AR). Twenty-four consecutive patients (28 hips) suffering from osteoarthritis or other degenerative hip disease underwent AD-MSC hip injection with a minimum 18 months follow up available for inclusion in the study. Four patients underwent bilateral AD-MSC hip treatment. 8 were male and 16 were female. Patient demographics are presented in Table 1. No patients were lost to follow-up. 4 patients did not reach minimum 18 months follow up and were excluded. Patients underwent clinical and radiological (x-ray) pre-operative assessment. Patients were considered for injection therapy if they were suffering from hip pain, non-responsive to conservative treatment and had grade II-III according to Kellegren-Lawrence radiographic score. Patients were included in this study if they had a minimum

of 18 months follow-up and consented to participation. Patients were excluded if they had grade 1 or 4 according to Kellegren-Lawrence radiographic score, rheumatologic diseases, infection, avascular necrosis of the femoral head; and previous surgery in the affected joint.

## Surgical technique

Surgery was undertaken using deep sedation without any additional peripheral nerve blocks. Each patient received a 4 mL intra-articular adipose-derived autologous injection. The tissue was harvested from the abdominal pannus through a 3 mm caliber lipoaspirating cannula, after infiltration with Klein solution. The adipose tissue was processed with a mechanical non-enzymatic method proven to be effective in isolating a fluid and a uniform product containing many adipose-derived stem cells and stromal vascular fraction (Lipogems™) [8]. No patients had post-operative complications.

## Post injection rehabilitation

The patients were encouraged to swim and cycle to reduce maintain range of motion whilst restricting impact loading.

## Follow-up method

Patients were assessed preoperatively, at 6-, 12- and 18-months post-treatment. The assessment was based on a 0 to 10 visual analogue scale (VAS) to quantify the pain and Harris hip score (HHS). The HHS has a maximum of 100 points: pain (44 points), function (47 points), range of motion (5 points), and deformity (4 points). HHS total score of <70 is considered poor, 70-80 is fair, 80-90 is good and >90 is excellent. Failure was defined as any HHS total score under 70 at 6 months follow-up.

## Statistical analysis

Statistical analyses were performed using SPSS Version 13.0 (IBM Corporation, USA). Demographic and outcome scores were presented as mean  $\pm$  standard deviation (SD). Comparison of outcome measures between the pre-operative and post-operative periods and between the two subgroups was performed using the Mann-Whitney test. Statistical significance was set at a p-value of <0.01.

## Results

The mean age of the patients was  $64 \pm 8.5$  years. There were 8 male patients and 16 female patients. Demographic information is show in table 1.

**Table 1:** Demographic

<b>Numbers of patients</b>	24
<b>Age</b>	64 ± 8.5
<b>MALE/FEMALE</b>	8/16
<b>HIPS</b>	28
<b>K-L II / K- L III</b>	15/13

K-L II: Kellegren-Lawrence grade II; K-L III: Kellegren-Lawrence grade III; Age is expressed in (mean and standard deviation).

All of the patients cooperated with the aforementioned post-operative instructions and rehabilitation guidelines. The mean pre-operative VAS-based pain score was 6.3 ± 1.1 and showed significant improvement at 6 months. At 12 and 18 months the VAS score maintained a good outcome

of 3.2 ± 2.2 and 3.4 ± 2.3, respectively. All scores at 6,12 and 18 months of follow-up showed a statistically significant improvement (p<0.01) compared to baseline across the cohort. Similar results for the two subgroups have been illustrated in Table 2.

**Table 2:**

	VAS				P-Value		
	Pre-operative	6 month follow-up	12 month Follow-up	18 month Follow-up	p-value 6 month	p-value 12 month	p-value 12 month
<b>TOTAL</b>	6.3 ± 1.1	2.9 ± 1.8	3.2 ± 2.2	3.4 ± 2.3	<.01	<.01	<.01
<b>Group K-L II</b>	5.6 ± 0.8	2.8 ± 1.5	2.7 ± 2.2	3.2 ± 2.2	<.01	<.01	<.01
<b>Group K-L III</b>	7.0 ± 1.0	3.1 ± 2.1	3.7 ± 2.2	3.8 ± 2.3	<.01	<.01	<.01
<b>p-value</b>	<.01	.37*	.13*	.15*			

VAS, visual analog scale; K-L II: Kellegren-Lawrence grade II; K-L III: Kellegren-Lawrence grade III; \* not significant difference between the two groups.

The mean pre-operative HHS was 65.9 ± 2.6 (<70 in twenty-six hips and 70-79 in two hips), the mean 6 months post-operative HHS was 83.7 ± 7.7 (< 70 in four hips, 70-79 in two hips, 80-89 in twenty patients and >90 in two), the

mean 12- and 18-month post-operative HHS was 82.5 ± 8.8 and 81.5 ± 6.8, respectively, maintaining good or excellent results in twenty hips. Similar results for the two subgroups are presented in Table 3.

**Table 3:**

	Harris hip score				p-Value		
	Pre-operative	6 month follow-up	12 month Follow-up	18 month Follow-up	p-value 6 month	p-value 12 month	p-value 12 month
<b>TOTAL</b>	65.9 ± 2.6	83.7 ± 7.7	82.5 ± 8.8	81.5 ± 6.8	<.01	<.01	<.01
<b>Group K-L II</b>	67.2 ± 3.0	83.9 ± 6.8	83.2 ± 9.4	82.3 ± 6.4	<.01	<.01	<.01
<b>Group K-L III</b>	64.5 ± 0.4	83.4 ± 8.8	81.7 ± 8.5	80.5 ± 7.5	<.01	<.01	<.01
<b>p-value</b>	<.01	.45*	.33*	.28*			

K-L II: Kellegren-Lawrence grade II; K-L III: Kellegren-Lawrence grade III; \* not significant difference between the two groups.

There was no statistical difference between the Kellegren-Lawrence groups in terms of VAS or HHS score at 6, 12 and 18 months. Four hips, in three patients had unsatisfactory

results at 6 months follow-up, hence were considered failures (Table 4).

**Table 4.** Failure patients with unsatisfactory HSS score at 6 months.

Sex	Age at Surgery	Procedure	THR at final FU
Male	57	Bilateral hip	Yes
Female	58	Unilateral hip	Yes
Male	71	Unilateral hip	No

In total six hips, in five patients underwent arthroplasty at final follow up with two of them having good results at 12 months follow-up and one at 6 months follow-up. These were not considered failures as they had at least 6 months of decreasing hip pain post injection.

## Discussion

The increased interest in adipose stem cell injections for osteoarthritis is due to their potential to promote anti-inflammatory, angiogenic and anti-apoptotic factors. This may aid the re-balancing of the anabolic and catabolic pathways which fail in OA, reducing degradation, inflammation and joint pain. The main finding of this study is that the injection of adipose-derived stem cells (AD-MS) procedure is simple, economic, quick, minimally invasive, single-staged and safe. It provides good clinical outcome in term of VAS and HSS for early stages of hip osteoarthritis. The adipose MSC injection has already been proven successful in the knee but few studies reported the use of this cell therapy in the hip [9,10]; Dall'Oca reported good results in 6 patients graded 0-2 on the Tonnis grading scale, using MSC injection without the arthroscopic exploration. All patients showed an improvement in term of Harris hip score (HHS) and WOMAC scores at 6 months' post-op follow up visit [11]. Emadin et al. [12] reported good WOMAC scores at 6 and 12 months and an improvement of hip function in terms of walking distances. A recent systematic review provides evidence that autologous intra-articular mesenchymal stem cells therapy is safe with positive clinical outcomes. In particular, this review included 13 studies from bone marrow and 12 studies from adipose tissue (AD-MS). MSCs were administered into 523 knees, 61 foot/ankle joints, and 5 hips. The mean follow-up time was 24.4 months after MSC therapy. All studies reported improvement from baseline in at least one clinical outcome measure, and no study reported major adverse events attributable to MSC therapy [13]. Our reported results are similar to Dall'Oca's [11] results at 6 months follow up. The current study represents the largest case series with the longest follow-up reported in the literature using the AD-MS injections in the human hip. Moreover, it shows the ability to have good results in patients with grade III Kellegren-Lawrence hip osteoarthritis. There is no consensus on how much processed lipoaspirate volume should be used in the hip. We decided to use  $\leq 4$  mL of processed lipoaspirate because the volume of the hip joint

cavity is smaller than that of the knee. In opinion of the authors, the three patients that had unsatisfactory results post-injection was probably due to suboptimal adipose tissue or worse than anticipated hip degeneration. On the contrary, the patients who had good outcomes at 6 months which then worsened could have had excessive physical activity use and overload during the pain-free period which then resulted in subchondral bone damage. The major limitation with this study is its retrospective nature with lack of comparison group. In addition, there was no detailed imaging (such as MRI) that could help analyse the chondral quality of the hip joints. Currently, we do not know if mesenchymal cells have any ability to decrease or reverse the progression of OA. However, these injections could be a valid treatment in terms of symptom relief and quality of life improvement in hip osteoarthritis patients. It is imperative that future studies use quality methodology such as RCTs and measure the long-term effects such as quality of life and subsequent treatments.

## Conclusions

The injection of adipose-derived MSCs significantly improved the clinical scores of patients with early hip osteoarthritis. This study provides evidence of a new treatment of hip OA in selected patients without any adverse events related to the procedure. The ultimate proof of the clinical utility of this therapy can only come, however, from a prospective, randomized therapeutic trial.

### Ethics approval and consent to participate

This is a retrospective study. Patients were private patients. no ethics approval but all patients agreed to undergo evaluation scores after informed consent. All methods were carried out in accordance with relevant guidelines and regulations.

### Consent for publication

Not applicable

### Availability of data and material

The datasets during and/or analysed during the current study are available from the corresponding author on reasonable request

### Competing interests

The authors declare that they have no competing interests

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### Authors' contributions

All authors have read and approved the manuscript and have given substantial contributions to this work.

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